right to present the subject matter of claims 1-8 in a divisional application in accordance with 35 U.S.C. § 121.

II. **The Invention**

The present application claims priority from U.S. Patent Application Serial No. 07/800,549, filed November 27, 1991 (now U.S. Patent No. 5,266,331; issued November 30, 1993), through International Patent Application No. PCT/US92/10146 filed November 25, 1992.

The claims of U.S. Patent No. 5,266,331 are directed in part to solid controlled release oral dosage forms of oxycodone or a salt thereof dispersed in a controlled-release matrix. The oral dosage forms provide an in vitro dissolution rate as measured by the USP Paddle Method, (described in detail in the Specification at page 3, lines 20, et seq.) of: between about 12.5 and 42.5 % oxycodone is released after 1 hour; between about 25 and 55 % oxycodone is released after 2 hours; between about 45 and 75 % oxycodone is released after 4 hours; and between about 55 and 85 % oxycodone is released after 6 hours, the in vitro release rate being substantially independent of between pH 1.6 and 7.2 chosen such that the peak plasma level of oxycodone obtained in-vivo occurs between 2 and 4 hours after administration of the dosage form.

The presently claimed invention, on the other hand, is directed to formulations such as the above containing from about 10 to about 160 mg of oxycodone or a salt thereof which are chosen so that a mean maximum peak plasma concentration of

oxycodone of from about 6 to about 240 ng/ml is obtained in-vivo from a mean of about 2 to about 4.5 hours after administration and a mean minimum plasma concentration of from about 3 to about 30 ng/ml is obtained in-vivo from a mean of about 10 to about 14 hours after steady state conditions are achieved by repeated 12 hour administrations.

The present invention is directed in part to the surprising discovery that by choosing the above-identified parameters in the controlled-release formulation, it is possible to acceptably control pain over a substantially narrower dosage range than through the use of other opioid analgesics of similar chemical structure. Thus, Applicants have surprising found that even in the case of controlled-release opioid formulations having a similar in-vitro release profile, a much wider range of dosage of drug must be administered to the patient in order to achieve a satisfactory analgesic response over the requisite period of time. This is set forth, e.g., in the Specification at page 6, line 30, through page 7, line 3. Therein it is mentioned that the despite the fact that both control-release oxycodone and control-release morphine administered every 12 hours possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations presently claimed can be used over approximately 1/2 the dosage range as compared to commercially available controlled-release morphine formulations.

The above result is surprising and of extreme clinical importance in that the clinician is able to identify the dose of

oxycodone which will control pain in a wide variety of patient populations while reducing the duration of unacceptable pain that individual patients must endure during the opioid analgesic titration process. Furthermore, to the pharmaceutical manufacturer, the presently-claimed invention represents a step forward in the preparation of control-release dosage forms because now it is possible to adequately dose a wide range of patient populations with relatively few solid dosage forms. Previously, in view of the wide variability of doses needed to provide effective analgesia in such patients, a greater number of dosage forms having different amounts of opioid would have to be available to the clinician in order to correctly titrate these patients.

Additional beneficial results obtained by the presently-claimed invention are set forth throughout the Specification, and the Examiner's attention is respectfully directed to the same.

III. The Rejection under 35 U.S.C.§ 102(b)

The Examiner has rejected the subject matter of claims 9-11 under 35 U.S.C.§ 102(b), alleging that the claims are anticipated by U.S. Patent No. 4, 990; 341. The Examiner has stated that the '341 patent discloses opioid analgesics with the claimed release rate. The Examiner also directed Applicants to example 1 of the '341 patent.

The Examiner's rejection is respectfully believed to be in error primarily because the claimed invention is specifically

directed to oxycodone formulations and the '341 patent is specifically directed to hydromorphone formulations. No mention is made in this reference with regard to any opioid analgesics other than hydromorphone. Absolutely no reference is made or can be inferred with respect to oxycodone. It is well settled that in order to constitute anticipation, all material elements of the claim must be found in one prior art source. Since the '341 patent does not disclose the claimed oxycodone-based oral dosage forms, the rejection must be withdrawn.

Furthermore, it is respectfully submitted that one of ordinary skill in the art is provided no information indicative that controlled-release oxycodone formulations described and claimed herein with particular (in-vivo) mean peak and mean minimum plasma concentrations could have been predicted from the disclosure of the '341 patent concerning hydromorphone formulations.

The teaching of controlled-release matrix hydromorphone formulations set forth in the '341 patent does not provide one with the information necessary to design the claimed controlled-release oxycodone formulations which would provide surprising benefits (which would not be obtained via the hydromorphone formulations of the '341 patent). Moreover, the Goldie, et al. '341 patent is completely silent concerning the particular claimed in-vivo parameters claimed herein, which are specifically related to the surprising results obtained by the invention.

The in-vitro dissolution data, such as that found in the '341 patent, is but one of many factors which must be considered when formulating a particular drug composition. Such data are often not indicative of in-vivo effect, particularly in the case of opioids. One skilled in the art would not be able to accurately predict whether a hydromorphone formulation with the in-vitro dissolution profile taught in the '341 patent would provide the pharmacokinetics (including the mean peak and mean minimum plasma concentrations) and the pharmacodynamics (including the duration of effect to allow administrations every 12 hours) set forth in the claims of the presently considered patent application directed to oxycodone.

There is substantial variability in the pharmacology of opioids. In particular, the pharmacokinetics, or what the body does to one opioid, i.e., oxycodone, cannot be predicted based upon the information given for another opioid, i.e., hydromorphone. Furthermore, the pharmacodynamics, or what an opioid does to the body cannot be predicted by the information given for another opioid, i.e., hydromorphone.

In addition, it is known to those of ordinary skill that there is an unpredictable correlation between the pharmacokinetics and pharmacodynamics of a formulation. Indeed, this is a basic tenant of pharmacology. The relationship between the pharmacokinetics and pharmacodynamics of opioid analgesics is particularly complex and unpredictable because of many confounding factors. Opioid receptors occupy peripheral

pharmacokinetic compartments rather than the central compartment from which plasma concentrations are sampled. This leads to a lag time or disequilibrium between the time-course of plasma opioid levels and the time-action of the opioid. Mathematical modelling has been attempted to deal with this disequilibrium but the results are not predictive among different patients. In addition, different opioid effects are mediated by opioid receptors that are not part of the same pharmacokinetic compartment, but rather, are parts of different peripheral pharmacokinetic compartments. All of these factors prevent one from predicting the in-vivo oxycodone plasma levels claimed from the hydromorphone data found in the '341 patent.

Applicants have also reviewed Example 1 of the '341 patent as suggested by the Examiner. It is submitted that the hydromorphone formulation described therein has no value as an anticipatory teaching concerning the claimed invention nor is the claimed invention rendered obvious by the '341 patent.

In view of the '341 patent's lack of disclosure concerning oxycodone and further in view of the lack of predictability among opioid analgesics, it is respectfully requested that the Examiner reconsider and remove the rejection under 35 U.S.C. §102(b).

IV. **Notice of Draftperson's Patent Drawing Review**

The Notice (PTO 948) Included with the Office Action indicated that the drawings were not objected to. No other remarks concerning the drawings was made. Applicants submit

therefore that the drawings are in proper form and that no further action is required. If, on the other hand, it is determined that informalities exist, Applicants respectfully request that a further Notice (PTO 948) be transmitted to Applicants detailing the corrections required.

V. **Conclusion**

In view of the actions taken and arguments presented, it is respectfully submitted that the present application is now in condition for allowance.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,

STEINBERG, RASKIN & DAVIDSON, P.C.

By: _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/081,302	06/18/93	OSHLACK	B 93311

EXAMINER: WEBMAN, E
ART UNIT: 1502
PAPER NUMBER: 9

15M1/0612

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

DATE MAILED: 06/12/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 2/22/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ___ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 9-11 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9-11 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

'912 - 128

Claims 9-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,266,331. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claim is generic to the instant claims.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. *In re Vogel*, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d).

This application repeats a substantial portion of prior application Serial No. 07/800,549, filed November 27, 1991, and adds and claims additional disclosure not presented in the prior application. Since this application names an inventor or inventors named in the prior application, it may constitute a continuation-in-part of the prior application. Should applicant desire to obtain the benefit of the filing date of the prior application, attention is directed to 35 U.S.C. § 120 and 37 C.F.R. § 1.78.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120 as follows:

The continuing application must contain a specific reference to the parent application(s) in the specification.

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Edward J. Webman, whose telephone number is (703) 308-4432. The Examiner can normally be reached on Monday-Friday from 9:00 a.m. to 5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, T. K. Page, can be reached on (703) 308-2927. The fax number for this Group is (703) 305-5408.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-2351.

Edward J. Webman:cb
Patent Examiner

Friday, June 9, 1995

EDWARD J. WEBMAN
PRIMARY EXAMINER
GROUP 1500

MAIL ROOM SEP 13 1995 PAT. & TRADEMARK OFF.

10/Ac 9-12

93-311

UNITED STATES PATENT AND TRADEMARK OFFICE

Be: 10-12-

Examiner: E. Webman — Art Unit: 1502

Re: Application of: Benjamin OSHLACK, et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: **CONTROLLED RELEASE OXYCODONE COMPOSITIONS**

SEP 18 1995 RECEIVED

AMENDMENT

Hon. Commissioner of
Patents and Trademarks
Washington, D.C. 20231

September 12, 1995

Sir:

Responsive to the office action dated June 12 , 1995, please amend the application as follows:

IN THE SPECIFICATION:

After the title, insert --This Application is a continuation-in-part of U.S. Patent Application Serial No. 07/800,549, filed November 27, 1991, now U.S. Patent No. 5,266,331. --.

REMARKS

Applicants respectfully request that the above Amendment to the Specification be entered and made of record.

In the Office Action dated June 12, 1995, the Examiner rejected claims 9-11 for obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 5,266,331.

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to "Commissioner of Patents and Trademarks, Washington, D.C. 20231" on September 12 , 1995.

STEINBERG, RASKIN & DAVIDSON, P.C.

BY:

'912 - 131

In response to this rejection, a duly executed Terminal Disclaimer is being submitted herewith in order to overcome this rejection.

Additionally, the Examiner indicated that Applicants might desire to obtain the benefit of the filing date of the prior Application, Serial No. 07/800,546, filed November 27, 1991.

In response, it is noted that the specification has now been amended to make it clear that this Application is, indeed, a continuation-in-part of the above identified prior Application. This Amendment was made in order to complete the formal requirements to claim priority under 35 U.S.C. §120. An executed Supplemental Declaration reflecting the priority claim will be submitted in due course.

It is respectfully submitted that, in view of the changes made to the specification and the submission of the enclosed Terminal Disclaimer, that all of the outstanding issues have now been addressed and that this Application is now in condition for allowance. If, however, any further changes are deemed necessary, the Examiner is invited to contact the undersigned at the telephone number indicated below with any inquiry concerning this Amendment.

Respectfully submitted,

STEINBERG, RASKIN & DAVIDSON, P.C.

By: _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768–3800

110 - 148 GP 1502

Docket No. 200.93311

#11
MC
10/17/95

SEP 26 1995
RECEIVED

UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner:	E. Webman	Art Unit: 1502
Re: Application of:		Benjamin OSHLACK, et al.
Serial No.:		08/081,302
Filed:		June 18, 1993
For:		CONTROLLED RELEASE OXYCODONE COMPOSITIONS

TERMINAL DISCLAIMER IN APPLICATION

Hon. Commissioner of
Patents & Trademarks
Washington, D.C. 20231

September 11, 1995

Sir:

Martin Greene, Procurist of Euro-Celtique, S.A. represents that Euro-Celtique, S.A. is the Assignee of the entire right, title and interest in U.S. Patent No. 5,266,331, granted November 30, 1993, entitled "CONTROLLED RELEASE OXYCODONE COMPOSITIONS" as set out in the Assignment recorded at Reel 5932, Frame 0573, a copy of which is attached hereto as Exhibit A.

Martin Greene, Procurist of Euro-Celtique, S.A., also represents that Euro-Celtique, S.A. is the Assignee of the entire right, title and interest in the above-identified patent application Serial No. 08/081,302, filed on June 18, 1993 for "CONTROLLED RELEASE OXYCODONE COMPOSITIONS", Assignment recorded at Reel 6717, Frame 0689, a copy of which is attached hereto as Exhibit B.

I hereby certify that this correspondence and/or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to: "Commissioner of Patents and Trademarks, Washington, D.C. 20231" on 9/12/95
STEINBERG, RASKIN & DAVIDSON, P.C.
By Deborah Mayer

230 LC 09/22/95 08081302
1 148 110.00 CK

'912 - 133

Euro-Celtique, S.A. hereby disclaims the terminal part of any patent granted on the above identified application which would extend beyond the expiration date of Patent No. 5,266,331, granted November 30, 1993, and hereby agrees that any patent granted on the above identified application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to Patent No. 5,266,331, granted November 30, 1993, this agreement to run with any patent granted on the above identified application and to be binding upon the grantee, its successors or assigns.

Assignee does not disclaim any terminal part of any patent granted on the above-identified application prior to the expiration date of the full statutory term of Patent No. 5,266,331 in the event that it later: expires for failure to pay a maintenance fee, is held enforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321(a), has all claims canceled by a reexamination certificate, or is otherwise terminated prior to the expiration of its statutory term, except for the separation of legal title stated above.

Pursuant to 37 CFR §3.73(b), Assignee hereby certifies that the evidentiary documents have been reviewed, i.e., the Assignments attached hereto, and, to the best of Assignee's knowledge and belief, title is in the Assignee seeking to take this action.

The undersigned certifies that he is authorized by Assignee to executed the within Terminal Disclaimer on behalf of Assignee.

The statutory $110.00 fee for a disclaimer is submitted herewith. Any deficiency or overpayment should be charged or credited to Deposit Account No. 19-4210 of our legal representative, Steinberg, Raskin & Davidson, P.C. A duplicate copy of this sheet is enclosed.

Dated: September 11, 1995

By: _____
Martin Greene, Procurist
Euro-Celtique, S.A.

SEP 1995 PAT. & TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

RECEIVED
2 9 1993
STEINBERG & RASKIN

DATE: 11/03/93
TO: N04C

HAROLD D. STEINBERG
STEINBERG & RASKIN
93-311
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT BRANCH OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW.

PLEASE REVIEW ALL INFORMATION CONTAINED ON THIS NOTICE. THE INFORMATION CONTAINED ON THIS RECORDATION NOTICE REFLECTS THE DATA PRESENT IN THE PATENT ASSIGNMENT PROCESSING SYSTEM. IF YOU SHOULD FIND ANY ERRORS OR QUESTIONS CONCERNING THIS NOTICE, YOU MAY CONTACT THE EMPLOYEE WHOSE NAME APPEARS ON THIS NOTICE AT 703-308-9723. PLEASE SEND REQUEST FOR CORRECTION TO: U.S. PATENT AND TRADEMARK OFFICE, ASSIGNMENT BRANCH, NORTH TOWER BUILDING, SUITE 10C35, WASHINGTON, D.C. 20231

ASSIGNOR: DOC DATE: 05/14/93
OSHLACK, BENJAMIN

ASSIGNOR: DOC DATE: 05/14/93
CHASIN, MARK

ASSIGNOR: DOC DATE: 05/14/93
MINOGUE, JOHN JOSEPH

ASSIGNOR: DOC DATE: 05/14/93
KAIKO, ROBERT FRANCIS

RECORDATION DATE: 06/18/93 NUMBER OF PAGES 002 REEL/FRAME 6717/0689

DIGEST : ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE:
EUROCELTIQUE, S.A.
122 BOULEVARD DE LA PETRUSSE
LUXEMBOURG

SERIAL NUMBER 8-081302 FILING DATE 06/18/93
PATENT NUMBER ISSUE DATE 00/00/00

EXAMINER/PARALEGAL
ASSIGNMENT BRANCH
ASSIGNMENT/CERTIFICATION SERVICES DIVISION

'912 - 135

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO
08/081,302	06/18/93	BLACK,	

EXAMINER	
WEINMAN, E.	93311
ART UNIT	PAPER NUMBER
1102	12/B

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

DATE MAILED
12/26/95

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to PHONE CALL OF 12/18/95.
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 3-11.
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [ ] been filed in parent application Serial No. _____, filed on _____.
6. ☒ Note the attached Examiner's Amendment.
7. ☐ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☐ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:
- ✓ Examiner's Amendment
- _ Examiner Interview Summary Record, PTOL-413
- _ Reasons for Allowance
- _ Notice of References Cited, PTO-892
- _ Information Disclosure Citation, PTO-1449
- _ Notice of Informal Application, PTO-152
- _ Notice re Patent Drawings, PTO-948
- _ Listing of Bonded Draftsmen
- _ Other

PTOL-37 (REV. 4-89) *

USCOMM-DC 89-3789

'912 - 136

Authorization for this Examiner's Amendment was given in a telephone interview with C. M. Davidson on 12/18/95.

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Cancel claims 1 and 2.

Edward J. Webman
12/24/95

EDWARD J. WEBMAN
PRIMARY EXAMINER
GROUP 1500

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: Box ISSUE FEE
COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

96.

15M1/1226

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

NOTICE OF ALLOWANCE AND ISSUE FEE DUE

☐ Note attached communication from the Examiner.
☑ This notice is issued in view of applicant's communication filed _____

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
08/081,902	06/18/93	009	WEDMAN, R 1502	12/26/95

First Named Applicant: OSHLACK, BENJAMIN

TITLE OF INVENTION: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
99311	424/468.000	527	UTILITY	NO	$1250.00	03/26/96

THE APPLICATION IDENTIFIES ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.

THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.

HOW TO RESPOND TO THIS NOTICE:

I. Review the SMALL ENTITY Status shown above.
If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the patent and Trademark Office of the change in status, or
B. If the Status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:
A. Pay FEE DUE shown above, or
B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

II. Part B of this notice should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B should be completed and returned. If you are charging the ISSUE FEE to your deposit account, Part C of this notice should also be completed and returned.

III. All communications regarding this application must give series code (or filing date), serial number and batch number. Please direct all communication prior to issuance to Box ISSUE FEE unless advised to contrary.

IMPORTANT REMINDER: Patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

Page 1 of 2

'912 - 138

CJR

PART B—ISSUE FEE TRANSMITTAL 1250 142 30 561 B #24

MAILING INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE. Blocks 2 through 6 should be completed where appropriate. All further correspondence including the Issue Fee Receipt, the Patent, advance orders and notification of maintenance fees will be mailed to addressee entered in Block 1 unless you direct otherwise, by: (a) specifying a new correspondence address in Block 3 below; or (b) providing the PTO with a separate "FEE ADDRESS" for maintenance fee notifications with the payment of Issue Fee or thereafter. See reverse for Certificate of Mailing.

1. CORRESPONDENCE ADDRESS

MAIL ROOM JAN 19 1996 PAT. & TRADEMARK OFF. 73

15M1/1226

STEINBERG & RASKIN
1140 AVENUE OF THE AMERICAS
NEW YORK, NY 10036

2. INVENTOR(S) ADDRESS CHANGE (Complete only if there is a change)

INVENTOR'S NAME

Street Address

City, State and ZIP Code

CO-INVENTOR'S NAME

Street Address

City, State and ZIP Code

☐ Check if additional changes are on reverse side

SERIES CODE/SERIAL NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT		DATE MAILED
08/081,302	06/18/93	009	WEBMAN, E	1502	12/26/95

First Named Applicant: OSHLACK, BENJAMIN

TITLE OF INVENTION: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
93311	424-468.000	S27	UTILITY	NO	$1250.00	03/26/96

3. Correspondence address change (Complete only if there is a change)
Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
Attn: Clifford M. Davidson

4. For printing on the patent front page, list the names of not more than 3 registered patent attorneys or agents OR, alternatively, the name of a firm having as a member a registered attorney or agent. If no name is listed, no name will be printed.
1 Steinberg, Raskin & Davidson, P.C.

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120 DB 01/30/96 08081302 1 561 30.00 CK

5. ASSIGNMENT DATA TO BE PRINTED ON THE PATENT (print or type)

(1) NAME OF ASSIGNEE: Euro-Celtique, S.A.

(2) ADDRESS: (CITY & STATE OR COUNTRY) 122, Bd de la Petrusse, L-2330 LUXEMBOURG

A. ☐ This application is NOT assigned.
☒ Assignment previously submitted to the Patent and Trademark Office.
☐ Assignment is being submitted under separate cover. Assignments should be directed to Box ASSIGNMENTS.

PLEASE NOTE: Unless an assignee is identified in Block 5, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the PTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

6a. The following fees are enclosed:
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6b. The following fees should be charged to:
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☒ Any Deficiencies in Enclosed Fees

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(Authorized Signature) [signature] (Date) 01/17/96

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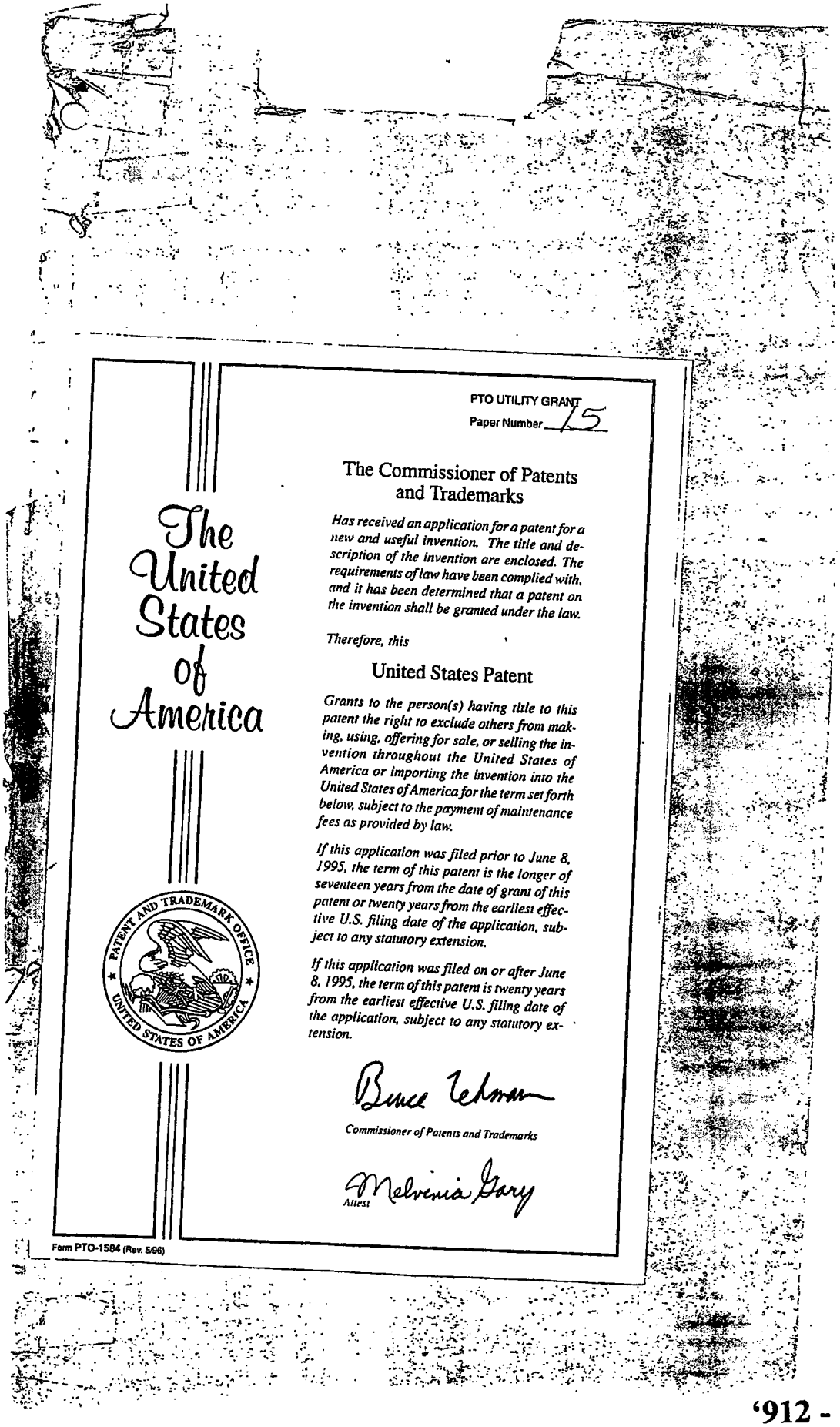

PTO UTILITY GRANT
Paper Number 15

The United States of America

The Commissioner of Patents and Trademarks

Has received an application for a patent for a new and useful invention. The title and description of the invention are enclosed. The requirements of law have been complied with, and it has been determined that a patent on the invention shall be granted under the law.

Therefore, this

United States Patent

Grants to the person(s) having title to this patent the right to exclude others from making, using, offering for sale, or selling the invention throughout the United States of America or importing the invention into the United States of America for the term set forth below, subject to the payment of maintenance fees as provided by law.

If this application was filed prior to June 8, 1995, the term of this patent is the longer of seventeen years from the date of grant of this patent or twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

If this application was filed on or after June 8, 1995, the term of this patent is twenty years from the earliest effective U.S. filing date of the application, subject to any statutory extension.

Bruce Lehman

Commissioner of Patents and Trademarks

Attest Melvinia Gary

Form PTO-1584 (Rev. 5/96)

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UNITED STATES PATENT & TRADEMARK OFFICE

Examiner: Spear, J. Art Unit: 1502

Re: Application of: Benjamin OSHLACK et al.
Serial No.: 08/081,302
Filed: June 18, 1993
For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

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PETITION

Hon. Commissioner of
Patents & Trademarks
Washington, D.C. 20231

February 13, 1996

00

Sir:

424/468

Applicants hereby petition for entry of the amendment pursuant to 37 C.F.R. 1.312, filed simultaneously herewith.

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"Express Mail" mailing label no.:EM521032515US
Date of deposit: February 13, 1996
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STEINBERG, RASKIN & DAVIDSON, P.C.
BY: Sharon Meyer

5,549,912

8.27

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This amendment is submitted in order to correct a transposition error which occurred prior to submission of the present application. In the claims as filed, independent claims 2 and 3 correctly set forth that for controlled release oxycodone formulations of from about 10 mg to about 160 mg oxycodone or a salt thereof, the formulations provides a mean minimum plasma concentration could come about 3 to 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

Due to an inadvertent transposition error, claims 7 and 9, which are also related to oxycodone formulations from about 10 to about 160 mg oxycodone or a salt thereof, state that the mean minimum plasma concentration is from about "3 to about 30 ng/ml" 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions. Accordingly, while claims 7 and 9 are not incorrect in that they each recite plasma levels which are desired, these claims should more properly reflect the mean minimum plasma levels possible for doses of oxycodone significantly greater than 40 mg.

The transposition error mentioned above was first noticed on February 12, 1996 by the undersigned.

It is respectfully submitted that the above paragraphs set forth good and sufficient reasons why the amendment is necessary and was not earlier presented. Accordingly, entry of the accompanying amendment is respectfully requested and earnestly solicited.

A check in the amount of $130.00 is attached to cover the Petition Fee. If any additional fees are deemed necessary at this time, the Commissioner is authorized to charge such fee to deposit account No. 19-4210.

200.93311

It is requested that the undersigned be contacted in the event that the deposit account is to be debited.

Respectfully submitted,

STEINBERG, RASKIN & DAVIDSON, P.C.

By _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

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UNITED STATES PATENT & TRADEMARK OFFICE

Examiner: Spear, J. Art Unit: 1502

Re: Application of: Benjamin OSHLACK et al.

Serial No.: 08/081,302

Filed: June 18, 1993

For: CONTROLLED RELEASE OXYCODONE COMPOSITIONS

AMENDMENT PURSUANT TO 1.312(a)

Hon. Commissioner of
Patents & Trademarks
Washington, D.C. 20231

February 13, 1996

Sir:

Please amend the above-identified application as follows:

IN THE CLAIMS:

Claim 7, line 16, change "30" to --120--;

Claim 9, line 18, change "30" to --120--.

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Date of deposit: February 13, 1996
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STEINBERG, RASKIN & DAVIDSON, P.C.
BY: [signature]

REMARKS

Entry of this amendment is respectfully requested. This amendment is accompanied by a Petition Under 1.312(b) and the appropriate fee. This amendment is submitted in order to correct a transposition error which occurred prior to submission of this application regarding the mean minimum plasma concentration for the oxycodone formulation of claims 7 and 9.

In the claims as filed, independent claims 2 and 3 correctly set forth that for controlled release oxycodone formulations of from about 10 mg to about 160 mg oxycodone or a salt thereof, the formulations provides a mean minimum plasma concentration could come about 3 to 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

Due to an inadvertent transposition error, claims 7 and 9, which are also related to oxycodone formulations from about 10 to about 160 mg oxycodone or a salt thereof, state that the mean minimum plasma concentration is from about "3 to about 30 ng/ml" 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions. Accordingly, while claims 7 and 9 are not incorrect in that they each recite plasma levels which are desired, these claims should more properly reflect the mean minimum plasma levels possible for doses of oxycodone significantly greater than 40 mg.

The transposition error mentioned above was first noticed on February 12, 1996 by the undersigned.

The Examiner is invited to contact the undersigned at the number provided below if he has any questions regarding this amendment.

200.93311

A check in the amount of $130.00 is attached to cover the Petition Fee. If any fees are deemed necessary at this time, the Commissioner is authorized to charge such fees to deposit account No. 19-4210.

Respectfully submitted,
STEINBERG, RASKIN & DAVIDSON, P.C.

By _____
Clifford M. Davidson
Reg. No. 32,728

Steinberg, Raskin & Davidson, P.C.
1140 Avenue of the Americas
New York, New York 10036
(212) 768-3800

PATENT QUERY CONTROL FORM

Series–Patent No. : 5527541 Prepared by JW

Serial No. : 08/1302 Date 5-7

Issue Date : 6-18 No. of queries

Examiner–GAU : WEBMAN 1502

JACKET (1-missing; 2-illegible; 3-incomplete; 4-invalid; 5-other)

		1	2	3	4	5
a	Patent–Serial No					
b	Applicant(s)					
c	Title					
d	Priority Data					
e	Continuing Data					
f	Searched					
g	PTO 46–7(270)					
h	PTO 46–42(892)					

		1	2	3	4	5
i	Claims Allowed					
j	Assignment					
k	Sheets & Figures					
l	Class-Subclass-GAU					
m	Abstract					
n	Disclaimer Date					
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PATENT QUERY CONTROL FORM

Series–Patent No. : 5527541 Prepared by JW

Serial No. : 081302 Date 5-1

Issue Date : 6-18 No. of queries

Examiner–GAU : WEBMAN 1502

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b	Applicant(s)					
c	Title					
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f	Searched					
g	PTO 46–7(270)					
h	PTO 46–42(892)					

		1	2	3	4	5
i	Claims Allowed					
j	Assignment					
k	Sheets & Figures					
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- m Other

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CYCLE 3				
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CYCLE 3						
CYCLE 4						

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US005549912A

United States Patent [19]

Oshlack et al.

[11] Patent Number: 5,549,912

[45] Date of Patent: *Aug. 27, 1996

[54] **CONTROLLED RELEASE OXYCODONE COMPOSITIONS**

[75] Inventors: **Benjamin Oshlack**, New York, N.Y.; **Mark Chasin**, Manalpan, N.J.; **John J. Minogue**, Mount Vernon, N.Y.; **Robert F. Kaiko**, Weston, Conn.

[73] Assignee: **Euro-Celtique, S.A.**, Luxembourg, Luxembourg

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,266,331.

[21] Appl. No.: **81,302**

[22] PCT Filed: **Nov. 25, 1992**

[86] PCT No.: **PCT/US92/10146**

§ 371 Date: **Jun. 18, 1993**

§ 102(e) Date: **Jun. 18, 1993**

[87] PCT Pub. No.: **WO93/10765**

PCT Pub. Date: **Jun. 10, 1993**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 800,549, Nov. 27, 1991, Pat. No. 5,266,331.

[51] Int. Cl.[6] **A61K 9/22**; A61K 9/26

[52] U.S. Cl. **424/468**; 424/469; 424/470; 424/486; 424/487; 424/488; 424/494; 424/496; 424/497; 424/498; 424/501; 424/502; 424/495

[58] Field of Search 424/486, 468–470, 424/487–88, 494, 496–498, 464–469

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,861,598	8/1989	Oshlack	424/470
4,990,341	2/1991	Goldie et al.	424/484

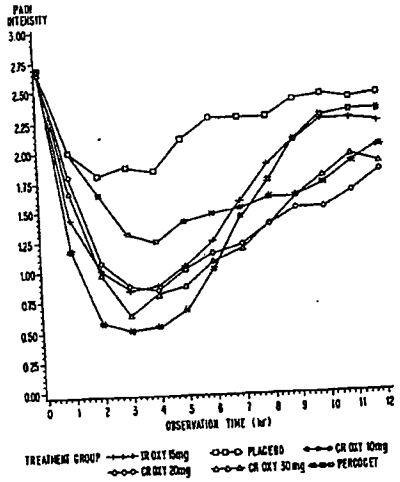
Primary Examiner—Edward J. Webman

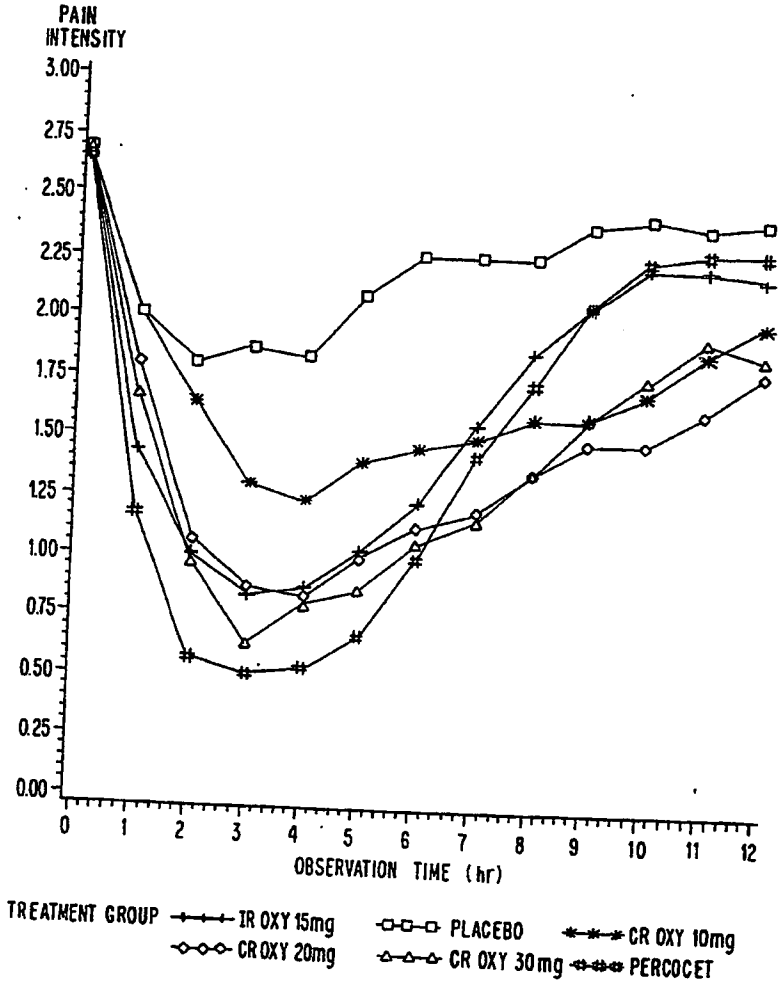
Attorney, Agent, or Firm—Steinberg, Raskin & Davidson, P.C.

[57] **ABSTRACT**

A method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients is disclosed whereby an oral solid controlled release dosage formulation having from about 10 to about 40 mg of oxycodone or a salt thereof is administered to a patient. The formulation provides a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions. Another embodiment is directed to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients by administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, such that a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions are achieved. Controlled release oxycodone formulations for achieving the above are also disclosed.

9 Claims, 5 Drawing Sheets

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2.50
2.25
2.00
1.75
1.50
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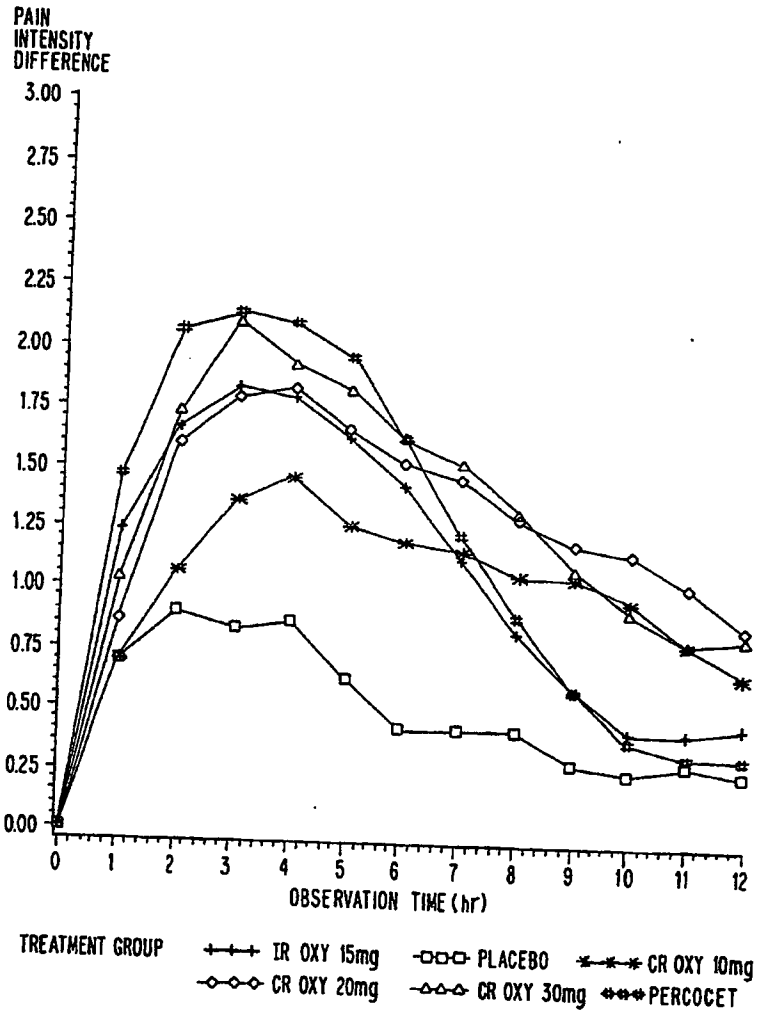
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
CR OXY 20mg
PLACEBO
CR OXY 30mg
CR OXY 10mg
PERCOCET

FIG. 1


PAIN INTENSITY DIFFERENCE
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2.75
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2.00
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0.25
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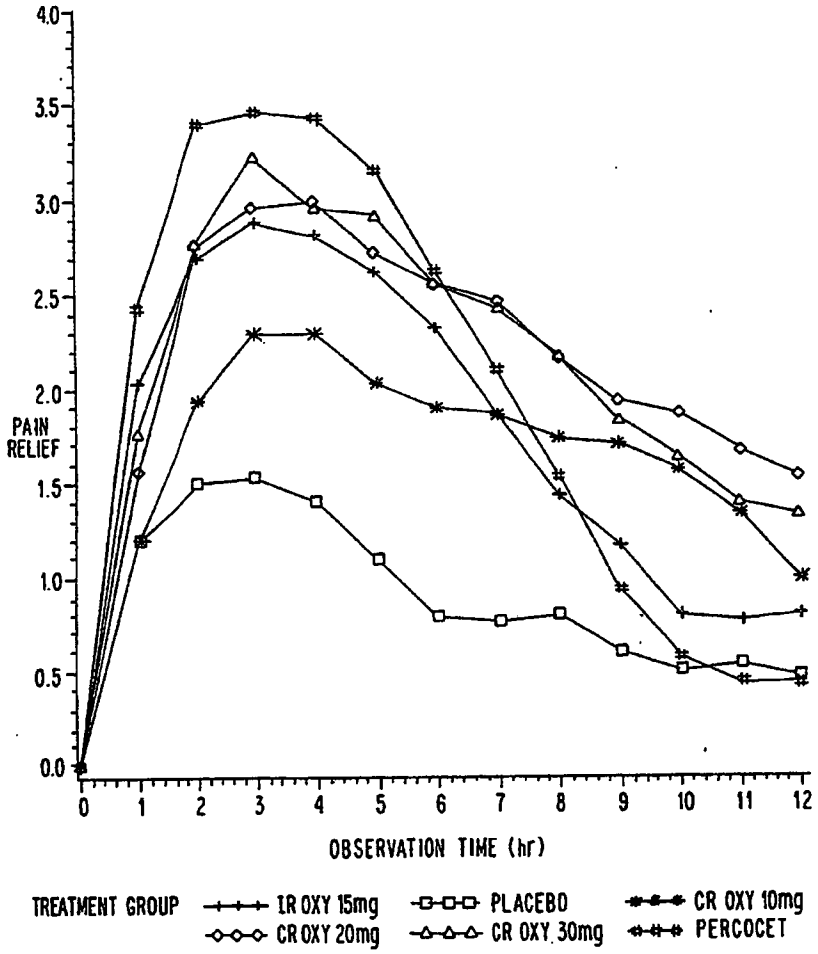
0
1
2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG.2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2
3
4
5
6
7
8
9
10
11
12
OBSERVATION TIME (hr)
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CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 3

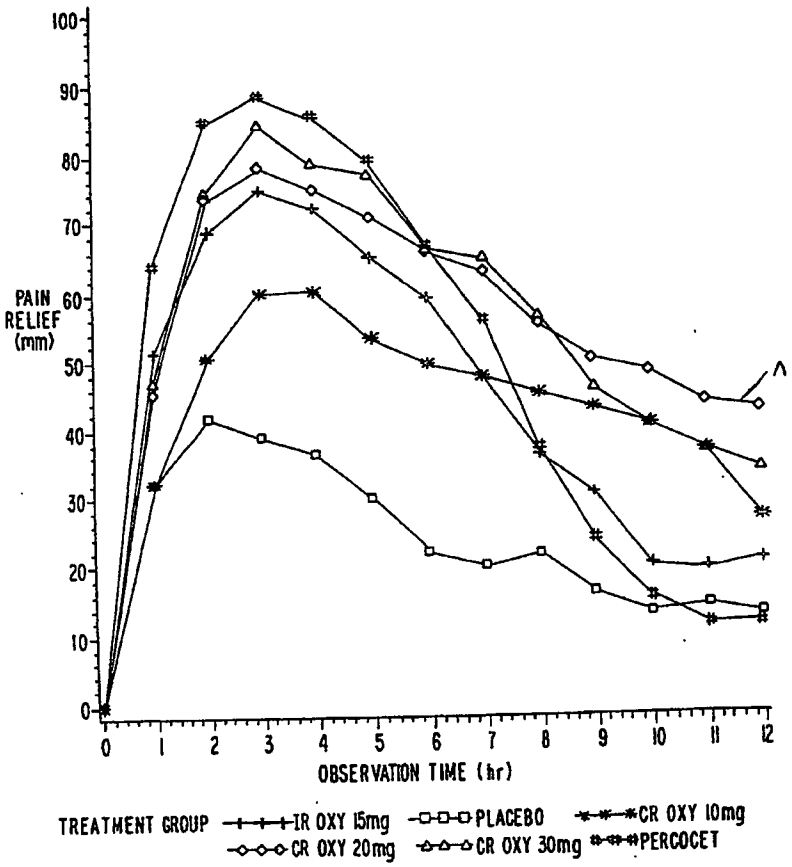
PAIN RELIEF (mm)
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10 11 12
OBSERVATION TIME (hr)
TREATMENT GROUP
IR OXY 15mg
PLACEBO
CR OXY 10mg
CR OXY 20mg
CR OXY 30mg
PERCOCET

FIG. 4

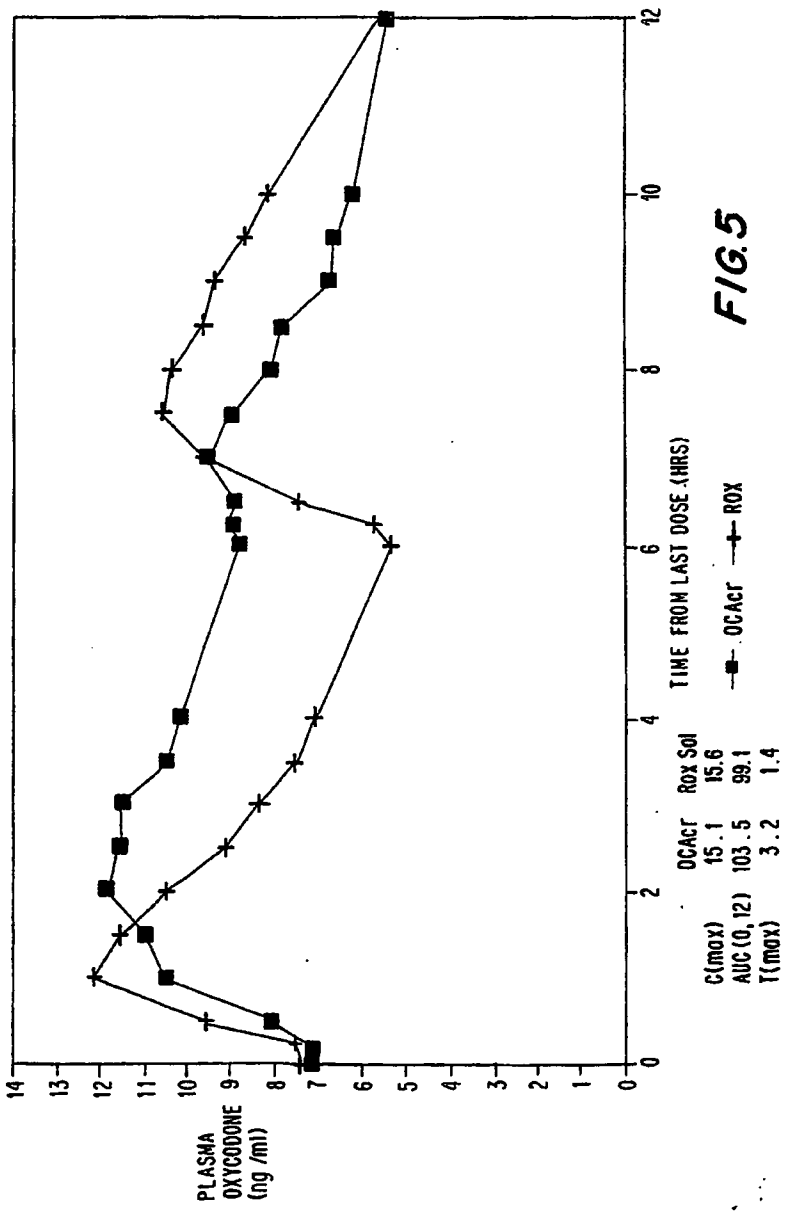
PLASMA OXYCODONE (ng /ml)
TIME FROM LAST DOSE (HRS)
OCAcr
ROX
C(max) OCAcr 15.1 Rox Sol 15.6
AUC(0,12) 103.5 99.1
T(max) 3.2 1.4

FIG.5

CONTROLLED RELEASE OXYCODONE COMPOSITIONS

This application is a continuation-in-part of U.S. patent application Ser. No. 07/800,549, filed Nov. 27, 1991, now U.S. Pat. No. 5,266,331.

BACKGROUND OF THE INVENTION

Surveys of daily dosages of opioid analgesics required to control pain suggest that an approximately eight-fold range in daily dosages is required to control pain in approximately 90% of patients. This extraordinary wide range in the appropriate dosage makes the titration process particularly time consuming and resource consuming, as well as leaving the patient without acceptable pain control for an unacceptably long duration.

In the management of pain with opioid analgesics, it has been commonly observed and reported that there is considerable inter-individual variation in the response to a given dose of a given drug, and, therefore, considerable variability among patients in the dosage of opioid analgesic required to control pain without unacceptable side effects. This necessitates considerable effort on the part of clinicians in establishing the appropriate dose in an individual patient through the time consuming process of titration, which requires careful assessment of both therapeutic and side effects and dosage adjustments over a period of days and sometimes longer before the appropriate dosage is determined. The American Pain Society's 3rd Edition of Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain explains that one should "be aware that the optimal analgesic dose varies widely among patients. Studies have shown that in all age groups, there is enormous variability in doses of opioids required to provide relief, even among opioid naive patients with identical surgical lesions . . . . This great variability underscores the need to write analgesic orders that include provision for supplementary doses, and to use intravenous boluses and infusions to provide rapid relief of severe pain . . . . Give each analgesic an adequate trial by dose titration . . . before switching to another drug."

An opioid analgesic treatment which acceptably controls pain over a substantially narrower daily dosage range would, therefore, substantially improve the efficiency and quality of pain management.

It has previously been known in the art that controlled release compositions of opioid analgesics such as morphine, hydromorphone or salts thereof could be prepared in a suitable matrix. For example, U.S. Pat. No. 4,990,341 (Goldie), also assigned to the assignee of the present invention, describes hydromorphone compositions wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., is between 12.5 and 42.5% (by wt) hydromorphone released after 1 hour, between 25 and 55% (by wt) released after 2 hours, between 45 and 75% (by wt) released after 4 hours and between 55 and 85% (by wt) released after 6 hours.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a method for substantially improving the efficiency and quality of pain management.

It is another object of the present invention to provide an opioid analgesic formulation which substantially improves the efficiency and quality of pain management.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the approximately eight-fold range in daily dosages required to control pain in approximately 90% of patients.

It is another object of the present invention to provide a method and formulation(s) which substantially reduce the variability in daily dosages and formulation requirements necessary to control pain in substantially all patients.

It is yet another object of the present invention to provide a method for substantially reducing the time and resources need to titrate patients requiring pain relief on opioid analgesics.

It is yet another object of the present invention to provide controlled release opioid formulations which have substantially less inter-individual variation with regard to the dose of opioid analgesic required to control pain without unacceptable side effects.

The above objects and others are attained by virtue of the present invention, which is related to a solid controlled release oral dosage form, the dosage form comprising from about 10 to about 40 mg of oxycodone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle Method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C. is between 12.5 and 42.5% (by wt) oxycodone released after 1 hour, between 25 and 56% (by wt) oxycodone released after 2 hours, between 45 and 75% (by wt) oxycodone released after 4 hours and between 55 and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH, such that the peak plasma level of oxycodone obtained in vivo occurs between 2 and 4.5 hours after administration of the dosage form.

USP Paddle Method is the Paddle Method described, e.g., in U.S. Pharmacopoeia XXII (1990).

In the present specification, "substantially independent of pH" means that the difference, at any given time, between the amount of oxycodone released at, e.g., pH 1.6, and the amount released at any other pH, e.g., pH 7.2 (when measured in vitro using the USP Paddle Method at 100 rpm in 900 ml aqueous buffer), is 10% (by weight) or less. The amounts released being, in all cases, a mean of at least three experiments.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in approximately 90% of patients, comprising administering an oral solid controlled release dosage formulation comprising from about 10 to about 40 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to a method for substantially reducing the range in daily dosages required to control pain in substantially all patients, comprising administering an oral solid controlled release dosage formulation comprising up to about 160 mg of oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of up to about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated "q12h" (i.e., every 12 hour) administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

The present invention is further related to controlled release oxycodone formulations comprising up to about 160 mg oxycodone or a salt thereof, said formulations providing a mean maximum plasma concentration of oxycodone up to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration up to about 120 ng/ml from about 10 to about 14 hours after repeated q12h administration through steady-state conditions.

BRIEF DESCRIPTION OF THE DRAWINGS

The following drawings are illustrative of embodiments of the invention and are not meant to limit the scope of the invention as encompassed by the claims.

FIGS. 1–4 are graphs showing the time-effect curves for pain intensity differences and pain relief for Example 17;

FIG. 5 is a graph showing the mean plasma oxycodone concentration for a 10 mg controlled release oxycodone formulation prepared in accordance with the present invention and a study reference standard.

DETAILED DESCRIPTION

It has now been surprisingly discovered that the presently claimed controlled release oxycodone formulations acceptably control pain over a substantially narrower, approximately four-fold (10 to 40 mg every 12 hours—around-the-clock dosing) in approximately 90% of patients. This is in sharp contrast to the approximately eight-fold range required for approximately 90% of patients for opioid analgesics in general.

The use of from about 10 mg to about 40 mg of 12-hourly doses of controlled-release oxycodone to control pain in approximately 90% of patients relative to a wider dosage range of other mu-agonist analgesics, indicated for moderate to severe pain, is an example of the unique characteristics of the present invention. It should also be appreciated that the remaining 10% of patients would also be successfully managed with 12-hourly controlled-release oxycodone over a relatively narrower dosage range than with the use of other similar analgesics. Substantially all of those remaining 10% of patients not managed with controlled release oxycodone, 10 mg to 40 mg every 12 hours, would be managed using dosages of greater than 40 mg every 12 hours through 160 mg every 12 hours utilizing any one of a number or multiples of formulation strengths such as 10, 20, 40, 80 and 160 mg unit dosages or combinations thereof. In contrast, the use of other similar analgesics such as morphine would require a wider range of dosages to manage the remaining 10% of patients. For example, daily dosages of oral morphine equivalents in the range of 1 gram to more than 20 grams have been observed. Similarly, wide dosage ranges of oral hydromorphone would also be required.

Morphine, which is considered to be the prototypic opioid analgesic, has been formulated into a 12 hour controlled-release formulations (i.e., MS Contin® tablets, commercially available from Purdue Pharma, L.P.). Despite the fact that both controlled-release oxycodone and controlled release morphine administered every 12 hours around-the-clock possess qualitatively comparable clinical pharmacokinetic characteristics, the oxycodone formulations of the presently claimed invention can be used over approximately ½ the dosage range as compared to commercially available controlled release morphine formulations (such as MS Contin®) to control 90% of patients with significant pain.

Repeated dose studies with the controlled release oxycodone formulations administered every 12 hours in comparison with immediate release oral oxycodone administered every 6 hours at the same total daily dose result in comparable extent of absorption, as well as comparable maximum and minimum concentrations. The time of maximum concentration occurs at approximately 2–4.5 hours after oral administration with the controlled-release product as compared to approximately 1 hour with the immediate release product. Similar repeated dose studies with MS Contin® tablets as compared to immediate release morphine provide for comparable relative results as with the controlled release oxycodone formulations of the present invention.

There exists no substantial deviation from parallelism of the dose-response curves for oxycodone either in the forms of the controlled release oxycodone formulations of the present invention, immediate release oral oxycodone or parenteral oxycodone in comparison with oral and parenteral opioids with which oxycodone has been compared in terms of dose-response studies and relative analgesic potency assays. Beaver, et al., "Analgesic Studies of Codeine and Oxycodone in Patients with Cancer. II. Comparisons of Intramuscular Oxycodone with Intramuscular Morphine and Codeine", J. Pharmacol. and Exp. Ther., Vol. 207, No. 1, pp. 101–108, reported comparable dose-response slopes for parenteral oxycodone as compared to parenteral morphine and comparable dose-response slopes for oral as compared to parenteral oxycodone.

A review of dose-response studies and relative analgesic assays of mu-agonist opioid analgesics, which include oxycodone, morphine, hydromorphone, levorphanol, methadone, meperidine, heroin, all indicate no significant deviation from parallelism in their dose response relationships. This is so well established that it has become an underlining principal providing for establishing relative analgesic potency factors and dose ratios which are commonly utilized when converting patients from one mu-agonist analgesic to another regardless of the dosage of the former. Unless the dose-response curves are parallel, conversion factors would not be valid across the wide range of dosages involved when substituting one drug for another.

The clinical significance provided by the controlled release oxycodone formulations of the present invention at a dosage range from about 10 to about 40 mg every 12 hours for acceptable pain management in approximately 90% of patients with moderate to severe pain, as compared to other opioid analgesics requiring approximately twice the dosage range provides for the most efficient and humane method of managing pain requiring repeated dosing. The expertise and time of physicians and nurses, as well as the duration of unacceptable pain patients must endure during the opioid analgesic titration process is substantially reduced through the efficiency of the controlled release oxycodone formulations of the present invention.

It is further clinically significant that a dose of about 80 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately 95% of patients with moderate to severe

pain, and that about 160 mg controlled release oxycodone administered every 12 hours will provide acceptable pain relief management in, e.g., approximately all patients with moderate to severe pain.

In order to obtain a controlled release drug dosage form having at least a 12 hour therapeutic effect, it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4–8 hours after administration (in a single dose study). The present inventors have surprisingly found that, in the case of oxycodone, a peak plasma level at between 2–4.5 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of oxycodone) in the normal period of up to 2 hours after administration.

A further advantage of the present composition, which releases oxycodone at a rate that is substantially independent of pH, is that it avoids dose dumping upon oral administration. In other words, the oxycodone is released evenly throughout the gastrointestinal tract.

The present oral dosage form may be presented as, for example, granules, spheroids or pellets in a capsule or in any other suitable solid form. Preferably, however, the oral dosage form is a tablet.

The present oral dosage form preferably contains between 1 and 500 mg, most especially between 10 and 160 mg, of oxycodone hydrochloride. Alternatively, the dosage form may contain molar equivalent amounts of other oxycodone salts or of the oxycodone base.

The present matrix may be any matrix that affords in vitro dissolution rates of oxycodone within the narrow ranges required and that releases the oxycodone in a pH independent manner. Preferably the matrix is a controlled release matrix, although normal release matrices having a coating that controls the release of the drug may be used. Suitable materials for inclusion in a controlled release matrix are

(a) Hydrophilic polymers, such as gums, cellulose ethers, acrylic resins and protein derived materials. Of these polymers, the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic polymer.

(b) Digestible, long chain (C_8–C_{50}, especially C_{12}–C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes. Hydrocarbons having a melting point of between 25° and 90° C. are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The oral dosage form may contain up to 60% (by weight) of at least one polyalkylene glycol.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}–C_{36}, preferably C_{14}–C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol.

The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose and, especially, hydroxyethyl cellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxycodone release required. Preferably however, the oral dosage form contains between 5% and 25%, especially between 6.25% and 15% (by wt) of the at least one hydroxyalkyl cellulose.

The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of oxycodone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one preferred embodiment, the controlled release composition comprises from about 5 to about 25% acrylic resin and from about 8 to about 40% by weight aliphatic alcohol by weight of the total dosage form. A particularly preferred acrylic resin comprises Eudragit® RS PM, commercially available from Rohm Pharma.

In the present preferred dosage form, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the oxycodone from the formulation. A ratio of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferred between 1000 and 15000 especially between 1500 and 12000.

Another suitable controlled release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

As an alternative to a controlled release matrix, the present matrix may be a normal release matrix having a coat that controls the release of the drug. In particularly preferred embodiments of this aspect of the invention, the present dosage form comprises film coated spheroids containing active ingredient and a non-water soluble spheronising agent. The term spheroid is known in the pharmaceutical art and means a spherical granule having a diameter of between 0.5 mm and 2.5 mm especially between 0.5 mm and 2 mm.

The spheronising agent may be any pharmaceutically acceptable material that, together with the active ingredient, can be spheronised to form spheroids. Microcrystalline cellulose is preferred.

A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). According to a preferred aspect of the present invention, the film coated spheroids contain between 70% and 99% (by wt), especially between 80% and 95% (by wt), of the spheronising agent, especially microcrystalline cellulose.

In addition to the active ingredient and spheronising agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxy propyl cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose.

The spheroids are preferably film coated with a material that permits release of the oxycodone (or salt) at a controlled rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other ingredients, the in-vitro release rate outlined above (between 12.5% and 42.5% (by wt) release after 1 hour, etc.).

The film coat will generally include a water insoluble material such as

(a) a wax, either alone or in admixture with a fatty alcohol,

(b) shellac or zein,

(c) a water insoluble cellulose, especially ethyl cellulose,

(d) a polymethacrylate, especially Eudragit®.

Preferably, the film coat comprises a mixture of the water insoluble material and a water soluble material. The ratio of water insoluble to water soluble material is determined by, amongst other factors, the release rate required and the solubility characteristics of the materials selected.

The water soluble material may be, for example, polyvinylpyrrolidone or, which is preferred, a water soluble cellulose, especially hydroxypropylmethyl cellulose.

Suitable combinations of water insoluble and water soluble materials for the film coat include shellac and polyvinylpyrrolidone or, which is preferred, ethyl cellulose and hydroxypropylmethyl cellulose.

In order to facilitate the preparation of a solid, controlled release, oral dosage form according to this invention there is provided, in a further aspect of the present invention, a process for the preparation of a solid, controlled release, oral dosage form according to the present invention comprising incorporating hydromorphone or a salt thereof in a controlled release matrix. Incorporation in the matrix may be effected, for example, by

(a) forming granules comprising at least one water soluble hydroxyalkyl cellulose and oxycodone or a oxycodone salt,

(b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12}–C_{36} aliphatic alcohol, and

(c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxyalkyl cellulose/oxycodone with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the oxycodone.

The present solid, controlled release, oral dosage form may also be prepared, in the form of film coated spheroids, by

(a) blending a mixture comprising oxycodone or a oxycodone salt and a non-water soluble spheronising agent,

(b) extruding the blended mixture to give an extrudate,

(c) spheronising the extrudate until spheroids are formed, and

(d) coating the spheroids with a film coat.

The present solid, controlled release, oral dosage form and processes for its preparation will now be described by way of example only.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following examples illustrate various aspects of the present invention. They are not meant to be construed to limit the claims in any manner whatsoever.

EXAMPLE 1

Controlled Release Oxycodone HCl 30 mg Tablets—Aqueous Manufacture

The required quantities of oxycodone hydrochloride, spray-dried lactose, and Eudragit® RS PM are transferred into an appropriate-size mixer, and mixed for approximately 5 minutes. While the powders are mixing, the mixture is granulated with enough water to produce a moist granular mass. The granules are then dried in a fluid bed dryer at 60° C., and then passed through an 8-mesh screen. Thereafter, the granules are redried and pushed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C., and while the granules are mixing, the melted stearyl alcohol is added. The warm granules are returned to the mixer.

The coated granules are removed from the mixer and allowed to cool. The granules are then passed through a 12-mesh screen. The granulate is then lubricated by mixing the required quantity of talc and magnesium stearate in a suitable blender. Tablets are compressed to 375 mg in weight on a suitable tableting machine. The formula for the tablets of Example 1 is set forth in Table 1 below:

TABLE 1

Formula of Oxycodone HCl 30-mg Tablets

Component	mg/Tablet	% (by wt)
Oxycodone Hydrochloride	30.0	8
Lactose (spray-dried)	213.75	57
Eudragit ® RS PM	45.0	12
Purified Water	q.s*	—
Stearyl Alcohol	75.0	20
Talc	7.5	2
Magnesium Stearate	3.75	1
Total:	375.0	100

*Used in manufacture and remains in final product as residual quantity only.

The tablets of Example 1 are then tested for dissolution via the USP Basket Method, 37° C., 100 RPM, first hour 700 ml gastric fluid at pH 1.2, then changed to 900 ml at 7.5. The results are set forth in Table 2 below:

TABLE 2

Dissolution of Oxycodone 30 mg Controlled Release Tablets

Time	% Oxycodone Dissolved
1	33.1
2	43.5
4	58.2

TABLE 2-continued

Dissolution of Oxycodone 30 mg Controlled Release Tablets	
Time	% Oxycodone Dissolved
8	73.2
12	81.8
18	85.8
24	89.2

EXAMPLE 2

Controlled Oxycodone HCl 10 mg Release Tablets—Organic Manufacture

The required quantities of oxycodone hydrochloride and spray dried lactose are transferred into an appropriate sized mixer and mix for approximately 6 minutes. Approximately 40 percent of the required Eudragit® RS PM powder is dispersed in Ethanol. While the powders are mixing, the powders are granulated with the dispersion and the mixing continued until a moist granular mass is formed. Additional ethanol is added if needed to reach granulation end point. The granulation is transferred to a fluid bed dryer and dried at 30° C.; and then passed through a 12-mesh screen. The remaining Eudragit® RS PM is dispersed in a solvent of 90 parts ethanol and 10 parts purified water; and sprayed onto the granules in the fluid bed granulator/dryer at 30° C. Next, the granulate is passed through a 12-mesh screen. The required quantity of stearyl alcohol is melted at approximately 60°–70° C. The warm granules are returned to the mixer. While mixing, the melted stearyl alcohol is added. The coated granules are removed from the mixer and allowed to cool. Thereafter, they are passed through a 12-mesh screen.

Next, the granulate is lubricated by mixing the required quantities of talc and magnesium stearate in a suitable blender. The granulate is then compressed to 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 2 (10 mg controlled release oxycodone) is set forth in Table 3 below:

TABLE 3

Formula of Oxycodone HCl 10 mg Controlled Release Tablets		
Component	Mg/Tablet	Percent (by wt)
Oxycodone hydrochloride	10.00	8
Lactose (spray-dried)	71.25	57
Eudragit ® RS PM	15.00	12
Ethanol	q.s.*	—
Purified Water	q.s.*	—
Stearyl Alcohol	25.00	20
Talc	2.50	2
Magnesium stearate	1.25	1
Total:	125.00 mg	100

*Used only in the manufacture and remains in final product as residual quantity only.

The tablets of Example 2 are then tested for dissolution via USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric (pH 1.2) then changed to 900 ml at pH 7.5.

The results are set forth in Table 4 below:

TABLE 4

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Dissolved
1	35.9
2	47.7
4	58.5
8	67.7
12	74.5
18	76.9
24	81.2

EXAMPLES 3–4

Controlled Release Oxycodone 10 and 20 mg Tablets (Aqueous Manufacture)

Eudragit® RS 30D and Triacetin® are combined while passing though a 60 mesh screen, and mixed under low shear for approximately 5 minutes or until a uniform dispersion is observed.

Next, suitable quantities of Oxycodone HCl, lactose, and povidone are placed into a fluid bed granulator/dryer (FBD) bowl, and the suspension sprayed onto the powder in the fluid bed. After spraying, the granulation is passed through a #12 screen if necessary to reduce lumps. The dry granulation is placed in a mixer.

In the meantime, the required amount of stearyl alcohol is melted at a temperature of approximately 70° C. The melted stearyl alcohol is incorporated into the granulation while mixing. The waxed granulation is transferred to a fluid bed granulator/dryer or trays and allowed to cool to room temperature or below. The cooled granulation is then passed through a #12 screen. Thereafter, the waxed granulation is placed in a mixer/blender and lubricated with the required amounts of talc and magnesium stearate for approximately 3 minutes, and then the granulate is compressed into 125 mg tablets on a suitable tableting machine.

The formula for the tablets of Example 3 is set forth in Table 5 below:

TABLE 5

Formula of Controlled Release Oxycodone 10 mg Tablets		
Component	Mg/Tablet	% (by wt)
Oxycodone Hydrochloride	10.0	8.0
Lactose (spray dried)	69.25	55.4
Povidone	5.0	4.0
Eudragit ® RS 30D (solids)	10.0*	8.0
Triacetin ®	2.0	1.6
Stearyl Alcohol	25.0	20.0
Talc	2.5	2.0
Magnesium Stearate	1.25	1.0
Total:	125.0	100.0

*Approximately 33.33 mg Eudragit ® RS 30D Aqueous dispersion is equivalent to 10 mg of Eudragit ® RS 30D dry substance.

The tablets of Example 3 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 6 below:

TABLE 6

Dissolution of Oxycodone 10 mg Controlled Release Tablets	
Hour	% Oxycodone Dissolved
1	38.0
2	47.5
4	62.0
8	79.8
12	91.1
18	94.9
24	98.7

The formula for the tablets of Example 4 is set forth in Table 7 below:

TABLE 7

Formula of Controlled Release Oxycodone 20 mg Tablets	
Component	Mg/Tablet
Oxycodone Hydrochloride	20.0
Lactose (spray dried)	59.25
Povidone	5.0
Eudragit ® RS 30D (solids)	10.0*
Triacetin ®	2.0
Stearyl Alcohol	25.0
Talc	2.5
Magnesium Stearate	1.25
Total:	125.0

The tablets of Example 4 are then tested for dissolution via the USP Basket Method at 37° C., 100 RPM, first hour 700 ml simulated gastric fluid at pH 1.2, then changed to 900 ml at pH 7.5. The results are set forth in Table 8 below:

TABLE 8

Dissolution of Oxycodone 20 mg Controlled Release Tablets	
Hour	% Oxycodone Dissolved
1	31
2	44
4	57
8	71
12	79
18	86
24	89

EXAMPLES 5–6

In Example 5, 30 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 1.

In Example 6, 10 mg controlled release oxycodone hydrochloride tablets are prepared according to the process set forth in Example 2.

Thereafter, dissolution studies of the tablets of Examples 5 and 6 are conducted at different pH levels, namely, pH 1.3, 4.56, 6.88 and 7.5.

The results are provided in Tables 9 and 10 below:

TABLE 9

Example 5 Percentage Oxycodone HCl 30 mg Tablets Dissolved Over Time							
pH	1	2	4	8	12	18	24
1.3	29.5	43.7	61.8	78.9	91.0	97.0	97.1
4.56	34.4	49.1	66.4	82.0	95.6	99.4	101.1
6.88	33.8	47.1	64.4	81.9	92.8	100.5	105.0
7.5	27.0	38.6	53.5	70.0	81.8	89.7	96.6

TABLE 10

Example 6 Percentage Oxycodone HCl - 10 mg Tablets Dissolved Over Time							
pH	1	2	4	8	12	18	24
1.3	25.9	41.5	58.5	73.5	85.3	90.7	94.2
4.56	37.8	44.2	59.4	78.6	88.2	91.2	93.7
6.88	34.7	45.2	60.0	75.5	81.4	90.3	93.9
7.5	33.2	40.1	51.5	66.3	75.2	81.7	86.8

EXAMPLES 7–12

In Examples 7–12, 4 mg and 10 mg oxycodone HCl tablets were prepared according to the formulations and methods set forth in the assignee's U.S. Pat. No. 4,990,341.

In Example 7, oxycodone hydrochloride (10.00 gm) was wet granulated with lactose monohydrate (417.5 gm) and hydroxyethyl cellulose (100.00 gm), and the granules were sieved through a 12 mesh screen. The granules were then dried in a fluid bed dryer at 50° C. and sieved through a 16 mesh screen.

Molten cetostearyl alcohol (300.0 gm) was added to the warmed oxycodone containing granules, and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen.

Purified Talc (15.0 gm) and magnesium stearate (7.5 gm) were then added and mixed with the granules. The granules were then compressed into tablets.

Example 8 is prepared in the same manner as Example 7; however, the formulation includes 10 mg oxycodone HCl/tablet. The formulas for Examples 7 and 8 are set forth in Tables 11 and 12, respectively.

TABLE 11

Formulation of Example 7		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Purified talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 12

Formulation of Example 8		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Lactose monohydrate	167.0	417.5
Hydroxyethylcellulose	40.0	100.0
Cetostearyl alcohol	120.0	300.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 9, 4 mg oxycodone HCl controlled release tablets are prepared according to the excipient formula cited in Example 2 of U.S. Pat. No. 4,990,341. The method of manufacture is the same as set forth in Examples 7 and 8 above. Example 10 is prepared according to Example 9, except that 10 mg oxycodone HCl is included per tablet. The formulas for Examples 9 and 10 are set forth in Tables 13 and 14, respectively.

TABLE 13

Formulation of Example 9		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	10.0
Anhydrous Lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

TABLE 14

Formulation of Example 14		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	25.0
Hydrous lactose	167.0	417.5
Hydroxyethylcellulose	30.0	75.0
Cetostearyl alcohol	90.0	225.0
Talc	6.0	15.0
Magnesium stearate	3.0	7.5

In Example 11, oxycodone 4 mg controlled release tablets are prepared with the same excipient formula cited in Example 3 of U.S. Pat. No. 4,990,341.

Oxycodone hydrochloride (32.0 gm) was wet granulated with lactose monohydrate (240.0 gm) hydroxyethyl cellulose (80.0 gm) and methacrylic acid copolymer (240.0 gm, Eudragit® L-100-55), and the granules were sieved through a 12 mesh screen. The granules were then dried in a Fluid Bed Dryer at 50° C. and passed through a 16 mesh screen.

The warmed oxycodone containing granules was added molten cetostearyl alcohol (240.0 gm), and the whole was mixed thoroughly. The mixture was allowed to cool in the air, regranulated and sieved through a 16 mesh screen. The granules were then compressed into tablets.

Example 12 is prepared in identical fashion to Example 11, except that 10 mg oxycodone HCl is included per tablet. The formulations for Examples 11 and 12 are set forth in Tables 15 and 16, respectively.

TABLE 15

Formulation of Example 11		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	4.0	32.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

TABLE 16

Formulation of Example 12		
Ingredient	mg/tablet	g/batch
Oxycodone hydrochloride	10.0	80.0
Lactose monohydrate	30.0	240.5
Hydroxyethylcellulose	10.0	80.0
Methacrylic acid copolymer	30.0	240.0
Cetostearyl alcohol	30.0	240.0

Next, dissolution studies were conducted on the tablets of Examples 7–12 using the USP basket method as described in the U.S. Pharmacopoeia XXII (1990). The speed was 100 rpm, the medium was simulated gastric fluid for the first hour followed by simulated intestinal fluid thereafter, at a temperature of 37° C. Results are given in Table 17.

TABLE 17

DISSOLUTION STUDIES OF EXAMPLES 7–12						
Time	% Oxycodone Dissolved					
(hrs)	Ex. 7	Ex. 8	Ex. 9	Ex. 10	Ex. 11	Ex. 12
1	23.3	25.5	28.1	29.3	31.3	40.9
2	35.6	37.5	41.5	43.2	44.9	55.6
4	52.9	56.4	61.2	63.6	62.1	74.2
8	75.3	79.2	83.7	88.0	82.0	93.9
12	90.7	94.5	95.2	100.0	91.4	100.0

EXAMPLES 13–16

Clinical Studies

In Examples 13–16, randomized crossover bioavailability studies were conducted employing the formulation of Examples 2 (organic manufacture) and 3 (aqueous manufacture).

In Example 13, a single dose fast/fed study was conducted on 24 subjects with oxycodone tablets prepared according to Example 3.

In Example 14, a steady-state study was conducted on 23 subjects after 12 hours with oxycodone tablets prepared according to Example 2, and compared to a 5 mg oxycodone immediate-release solution.

In Example 15, a single dose study was conducted on subjects using oxycodone tablets prepared according to Example 3, and compared to a 20 mg oxycodone immediate release solution.

In Example 16, a 12 subject single-dose study was conducted using 3x10 mg oxycodone tablets prepared according to Example 3, and compared to a 30 mg oxycodone immediate release solution.

The results of Examples 13–16 are set forth in Table 18.

TABLE 18

Example	Dosage	AUC ng/ml/hr	Cmax ng/ml	Tmax hr
13	10 mg CR Fast	63	6.1	3.8
	10 mg CR Fed	68	7.1	3.6
14	5 mg IR q6h	121	17	1.2
	10 mg CR q12h	130	17	3.2
15	20 mg IR	188	40	1.4
	2 × 10 mg CR	197	18	2.6
16	30 mg IR	306	53	1.2
	3 × 10 mg CR	350	35	2.6
	30 mg CR	352	36	2.9

IR denotes immediate-release oxycodone solution.
CR denotes controlled-release tablets

EXAMPLE 17

Clinical Studies

In Example 17, a single dose, double blind, randomized study determined the relative analgesic efficacy, the acceptability, and relative duration of action of an oral administration of controlled release oxycodone 10, 20 and 30 mg prepared according to the present invention (CR OXY) compared to immediate release oxycodone 15 mg (IR OXY), immediate release oxycodone 10 mg in combination with acetaminophen 650 mg (IR OXY/APAP) and placebo in 180 patients with moderate or severe pain following abdominal or gynecological surgery. Patients rated their pain intensity and pain relief hourly for up to 12 hours postdosing. Treatments were compared using standard scales for pain intensity and relief, and onset and duration of pain relief.

All active treatments were significantly superior to placebo for many of the hourly measures, and for sum pain intensity differences (SPID) and total pain relief (TOTPAR). A dose response was seen among the 3 dose levels of CR OXY for pain relief and peak pain intensity difference (PID), with CR OXY 20 mg and 30 mg being significantly better than the 10 mg dose. IR OXY was significantly superior to CR OXY 10 mg at hr 1 and 2. IR OXY/APAP was significantly superior to the 3 doses of CR OXY at hr 1, and to CR OXY 10 mg at hrs 2 through 5. Onset time was significantly shorter for the IR OXY and IR OXY/APAP treatment groups in comparison to the 3 CR OXY treatments. The distribution functions for duration of relief revealed significantly longer duration of relief for the three CR OXY doses than for IR OXY and IR OXY/APAP. No serious adverse experiences were reported. The results are more particularly reported in Table 19 below.

TABLE 19

	PATIENT DISPOSITION TREATMENT GROUP						
	IR OXY		CR OXY				
	15 mg	PLACEBO	10 mg	20 mg	30 mg	2 PERC*	TOTAL
Enrolled and Randomized to Study Treatment	31	31	30	30	30	30	182
Entered the Study Treatment Phase	31	31	30	30	30	30	182
Completed the Study	31	30	30	30	30	30	181
Discontinued from the Study	0	1	0	0	0	0	1
Excluded from Efficacy Analysis	0	1	0	0	0	0	1
Vomited prior to 1 hr post dose	1	0	0	0	0	0	1
Inadvertently received rescue during study	30	30	30	30	30	30	180
Analysis Population: Evaluable for Safety and Efficacy	31	31	30	30	30	30	182
Evaluable for Safety							

*2 tablets of Percocet ®

The time-effect curves for pain intensity, pain intensity differences and pain relief are shown in FIGS. 1–4. CR OXY 10 mg had significantly ($p<0.05$) lower pain intensity scores than the placebo-treated patients at hours 3–11 and lower pain scores than IR OXY 15 mg and Percocet® at hour 10. CR OXY 20 mg has significantly ($p<0.05$) lower pain

intensity scores compared to placebo at hours 2–11 and significantly ($p<0.05$) lower pain scores than CR OXY 10 mg, IR OXY 15 mg and Percocet at hours 9–11. CR OXY 30 mg had significantly ($p<0.05$) lower pain scores than placebo at hours 2–11 and lower pain scores than CR OXY 10 mg at hours 2, 3, and 5 and lower scores than Percocet® at hour 10.

For hourly pain relief scores categorical and visual analog scales (CAT and VAS), CR OXY 10 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 3–11 and higher relief scores than IR OXY and Percocet® at hour 10 (and Percocet® at hour 11). CR OXY 20 mg had significantly ($p<0.05$) higher relief scores than placebo at hours 2–12 and higher relief scores than Percocet® at hours 9–12. In addition, CR OXY had significantly ($p<0.05$) higher pain relief than IR OXY at hours 10–12. CR OXY 30 mg had significantly ($p<0.05$) higher pain relief scores than placebo at hours 2–12 and higher scores than Percocet® at hours 9–12 and IR OXY 15 mg at hour 10.

Each treatment group was significantly ($p<0.05$) better than placebo with respect to the sum of the pain intensity differences (SPID) and total pain relief (TOTPAR).

Duration of pain relief as measured by the patient stopwatch method showed that CR OXY 10 mg, 20 mg and 30 mg had significantly ($p<0.05$) longer duration of action compared to IR OXY 15 mg and 2 tablets Percocet®. In addition, the three controlled-release formulations had significantly ($p<0.05$) longer times to remedication compared to Percocet®.

Before remedication, a total of 104 (57%) of patients reported 120 adverse experiences. The most common were somnolence, fever, dizziness and headache.

Based upon the results of this study it is concluded that the controlled release oxycodone formulations of the present invention relieve moderate to severe postoperative pain, e.g., due to abdominal or gynecological surgery in women. There is a dose response noted in which placebo<10 mg<20 mg<30 mg CR OXY following a single dose. Onset of action occurred in one hour with peak effects noted from 2 to 5 hours and a duration of effect from 10 to 12 hours. In the chronic pain situation steady state dosing may prolong this effect. Side effects are expected and easily managed. Headache may be related to dose. Dizziness and somnolence were reported.

IR OXY 15 mg has an intermediate peak effect compared to controlled release oxycodone. Its duration of action is shorter (6–8 hours). Percocet® is quite effective in terms of onset, peak effect and safety. The duration of action is 6–8 hours.

In summary, CR OXY was clearly an effective oral analgesic, with a slower onset but a longer duration of effect than either IR OXY or IR OXY/APAP.

EXAMPLE 18

Clinical Studies

In Example 18, a steady state crossover trial was conducted in 21 normal male subjects comparing

a. CR OXY 10 mg administered every 12 hours (q12h); and

b. Roxicodone® oral solution 5 mg (ROX) administered every 6 hours (q6h),

Treatment (b) was the study reference standard. The average age was 34 years, height 176 cm and weight 75 kg. No unusual features were noted about the group.

FIG. 5 shows the mean plasma oxycodone concentrations for the two formulations over the 12 hour dosing interval. The results are summarized in Table 18 in terms of mean values, ratios of mean values and 90% confidence intervals.

As inspection of Table 18 reveals, with one exception, no significant differences were detected between the two formulations. The single exception is the mean t_{max} for CR OXY of 3.18 hours which, as expected for a controlled release formulation, significantly exceeded the ROX mean of 1.38 hours. Mean AUC-based bioavailability, (ROX=100%) was 104.4% with 90% confidence limits of 90.9 to 117.9%. Thus, the FDA specification of ±20% is met so that the study results support an assertion of equal oxycodone availability.

TABLE 20

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q 12H) AND ROXICODONE ® ORAL SOLUTION (5 mg q 6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
C_{max} (ng/mL)				
ARITH. MEAN (SD)	15.11(4.69)	15.57(4.41)	97.08	85.59–108.50
GEOMETRIC MEAN	14.43	15.01	95.14	
C_{min} (ng/mL)				
ARITH. MEAN (SD)	6.24(2.64)	6.47(3.07)	96.41	80.15–112.74
GEOMETRIC MEAN	5.62	5.83	96.48	
t_{max} (hrs)	3.18(2.21)	1.38(0.71)*	230.17	160.71–298.71
ARITH. MEAN (SD)				
AUC (0–12 hrs)				
ARITH. MEAN (SD)	103.50(40.03)	99.10(35.04)	104.44	90.92–117.94
GEOMETRIC MEAN	97.06	93.997	103.29	
% Swing ARITH. MEAN	176.36(139.0)	179.0(124.25)	98.53	62.06–134.92

TABLE 20-continued

SUMMARY OF PHARMACOKINETIC PARAMETERS FOR OXYCODONE FOLLOWING A SINGLE DOSE OF CR OXY (10 mg q 12h) AND ROXICODONE ® ORAL SOLUTION (5 mg q 6h)

PARAMETER	CR OXY	ROXICODONE SOLUTION	OXY/ ROXI (%)	90% CI*
(SD)				
% Fluctuation ARITH. MEAN (SD)	108.69(38.77)	117.75(52.47)	92.22	76.81–107.57
End Point ARITH. MEAN (SD)	−1.86(2.78)	−1.86(2.19)	99.97	117.77–22.23

*90% Confidence Interval
--Signicant Difference $p < 0.05$

EXAMPLE 19

Clinical Studies

In Example 19, twenty-four normal, healthy male subjects were enrolled in a randomized single-dose two-way cross-over study to compare the plasma oxycodone concentrations obtained after dosing with two controlled-release oxycodone 10 mg tablets versus 20 mg (20 ml of 5 mg/5 ml) of immediate release (IR) oxycodone hydrochloride solution. Twenty-three subjects completed the study and were eligible for analysis.

Plasma oxycodone concentrations were determined by a high performance liquid chromatographic procedure. Arithmetic Mean C_{max}, t_{max}, AUC, and half-lives calculated from individual plasma oxycodone concentration-versus-time data are set forth in Table 21:

TABLE 21

Pharmacokinetic Parameter	Reference Product IR Oxycodone 20 mg	Test Product CR Oxycodone 2 × 10 mg F. (%)		90% Confidence Interval
C_{max} (ng/ml)	41.60	18.62	44.75	32.5–57.0
t_{max} (hours)	1.30	2.62	200.83	169.8–232.6
AUC (0–36) (mg × hr/ml)	194.35	199.62	102.71	89.5–115.9
AUC (0–∞) (ng × hr/ml)	194.38	208.93	107.49	92.9–121.9
$t_{1/2(elim)}$ (hrs)	3.21	7.98*	249.15	219.0–278.8
$t_{1/2(abs)}$ (hrs)	0.35	0.92*	264.17	216.0–310.7

F. % = Oral bioavailability (CR oxycodone 2 × 10 mg/IR oxycodone 20 mg)
*Statistically significant ($p = 0.0001$)

For C_{max}, t_{max}, $t_{1/2}$(elim)and $t_{1/2}$(abs)there were statistically significant differences between the CR OXY and IR OXY. There were no statistically significant differences between the two treatments in the extent of absorption [AUC (0,36), AUC (0,∞). The 90% confidence interval for CR OXY relative to IR OXY relative was 89.5%–115.9% for AUC (0,36) and 92.9%–121.9% for AUC (0,∞). Based on the 90% confidence interval analysis, the controlled-release oxycodone tablets were equivalent in extent of absorption (AUC 0,36) to the immediate-release oxycodone solution. The controlled-release oxycodone absorption was slower by approximately 1.3 hours. No statistically significant differences were noted between the two treatments with reference to adverse experiences, none of which were considered clinically unusual for opiates for this type of study.

The above studies demonstrate a significant dose-response relationship utilizing the controlled release oxycodone formulations of the present invention at dosages of 10, 20 and 30 mg which does not deviate from parallelism with dose-response slopes for MS Contin in similarly designed well-controlled analgesic efficacy studies of MS Contin reported by Kaiko R. S., Van Wagoner D., Brown J., et al., "Controlled-Release Oral Morphine (MS Contin® Tablets MSC) in Postoperative Pain", Pain Suppl., 5:S149 1990, who compared 30, 60, 90, and 120 mg of MS Contin as compared with 10 mg of intramuscular morphine and placebo and Bloomfield, et al., "Analgesic Efficacy and Potency of Two Oral Controlled-Release Morphine Preparations", Clinical Pharmacology & Therapeutics, (in press), who compared 30 and 90 mg of MS Contin as compared to 30 and 90 mg of another controlled-release oral morphine preparation, Oramorph SR 30 mg tablets.

The examples provided above are not meant to be exclusive. Many other variations of the present invention would be obvious to those skilled in the art, and are contemplated to be within the scope of the appended claims.

What is claimed is:

1. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 to about 40 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 60 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

2. A controlled release oxycodone formulation for oral administration to human patients, comprising from about 10 mg to about 160 mg oxycodone or a salt thereof, said formulation providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

3. A solid controlled release oral dosage form, comprising

(a) oxycodone or a salt thereof in an amount from about 10 to about 160 mg;

(b) an effective amount of a controlled release matrix selected from the group consisting of hydrophilic polymers, hydrophobic polymers, digestible substituted or unsubstituted hydrocarbons having from about 8 to about 50 carbon atoms, polyalkylene glycols, and mixtures of any of the foregoing; and

(c) a suitable amount of a suitable pharmaceutical diluent, wherein said composition provides a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 120 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

4. The controlled release composition of claim 3, wherein said controlled release matrix comprises an acrylic resin.

5. A solid controlled release oral dosage form, comprising

(a) an analgesically effective amount of spheroids comprising oxycodone or a salt thereof and either a spheronising agent or an acrylic polymer or copolymer, such that the total dosage of oxycodone in said dosage form is from about 10 to about 160 mg;

(b) a film coating which controls the release of the oxycodone or oxycodone salt at a controlled rate in an aqueous medium, wherein said composition provides an in vitro dissolution rate of the dosage form;

said composition providing a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml from a mean of about 2 to about 4.5 hours after administration, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

6. The controlled release composition of claim 5, wherein said film coating comprises a water insoluble material selected from the group consisting of shellac or zein, a water insoluble cellulose, or a polymethacrylate.

7. A controlled release tablet for oral administration comprising from about 10 to about 160 mg oxycodone or an oxycodone salt dispersed in a controlled release matrix, said tablet providing an in-vitro dissolution of the dosage form, when measured by the USP Paddle Method at 100 rpm at 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37° C., between 12.5% and 42.5% (by wt) oxycodone released after 1 hour, between 25% and 55% (by wt) oxycodone released after 2 hours, between 45% and 75% (by wt) oxycodone released after 4 hours and between 55% and 85% (by wt) oxycodone released after 6 hours, the in vitro release rate being substantially independent of pH and chosen such that a mean maximum plasma concentration of oxycodone from about 6 to about 240 ng/ml is obtained in vivo from a mean of about 2 to about 4.5 hours after administration of the dosage form, and a mean minimum plasma concentration from about 3 to about 30 ng/ml from a mean of about 10 to about 14 hours after repeated administration every 12 hours through steady-state conditions.

8. A dosage form according to claim 7, wherein the in vitro dissolution rate is between 17.5% and 38% (by wt) oxycodone released after 1 hour, between 30% and 50% (by wt) oxycodone released after 2 hours, between 50% and 70% (by wt) oxycodone released after 4 hours and between 60% and 80% (by wt) oxycodone released after 6 hours.

9. A dosage form according to claim 7, wherein the in vitro dissolution rate is between 17.5% and 32.5% (by wt) oxycodone released after 1 hour, between 35% and 45% (by wt) oxycodone released after 2 hours, between 55% and 65% (by wt) oxycodone released after 4 hours and between 65% and 75% (by wt) oxycodone released after 6 hours.

* * * * *

PATENT APPLICATION FEE DETERMINATION RECORD

Effective October 1, 1992

Application or Docket Number 08/302

CLAIMS AS FILED - PART I

	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE	SMALL ENTITY FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY FEE
FOR							710
BASIC FEE				$355.00	OR		~~$710.00~~
TOTAL CLAIMS	11 minus 20 =	*	x$11=		OR	x$22=	
INDEPENDENT CLAIMS	7 minus 3 =	* 4	x 37=		OR	x 74=	296
MULTIPLE DEPENDENT CLAIM PRESENT			+115=		OR	+230=	
			TOTAL		OR	TOTAL	1006

* If the difference in column 1 is less than zero, enter "0" in column 2

CLAIMS AS AMENDED - PART II

AMENDMENT A	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 11	Minus	** 20	= —
Independent	* 7	Minus	*** 7	= —
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x 37=		OR	x 74=	
+ 115=		OR	+230=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x 37=		OR	x 74=	
+ 115=		OR	+ 230=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				

SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN SMALL ENTITY RATE	OTHER THAN SMALL ENTITY ADDITIONAL FEE
x$11=		OR	x$22=	
x 37=		OR	x 74=	
+115=		OR	+230=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

FORM PTO-875 (Rev.10-92)

Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

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PTO 1130 (REV 11/91)

U.S. DEPARTMENT OF COMMERCE– PATENT & TRADEMARK OFFICE

PACE DATA ENTRY CODING SHEET

1ST EXAMINER: L. Bates — DATE: 10/12

2ND EXAMINER: — DATE:

APPLICATION NUMBER	TYPE APPL	FILING DATE MONTH	DAY	YEAR	SPECIAL HANDLING	GROUP ART UNIT	CLASS	SHEETS OF DRAWING
07/081302	1	06	18	93	O	1205	514	5

TOTAL CLAIMS	INDEPENDENT CLAIMS	SMALL ENTITY?	FILING FEE	FOREIGN LICENSE	ATTORNEY DOCKET NUMBER
11	7	O	1006	1	9331

CONTINUITY DATA

CONTINUITY CODE	STATUS CODE	PARENT APPPLICATION SERIAL NUMBER	PARENT PATENT NUMBER	PARENT FILING DATE MONTH	DAY	YEAR
		0				
		0				
		0				
		0				
		0				

PCT/FOREIGN APPLICATION DATA

FOREIGN PRIORITY CLAIMED	COUNTRY CODE	PCT/FOREIGN APPLICATION SERIAL NUMBER	FOREIGN FILING DATE MONTH	DAY	YEAR
1	XXX	PCT/US92/10146	11	25	92

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SEARCHED

Class	Sub.	Date	Exmr.
424	486 468-470 487-88 494 496-498 464-465	8/94	[illegible]
TC	DATE	12/95	[illegible]

INTERFERENCE SEARCHED

Class	Sub.	Date	Exmr.
424	486-88 468-470 494 496-498 464-465	12/95	[illegible]

SEARCH NOTES

	Date	Exmr.
NONE 12/95	12/95	[illegible]

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POSITION		INIT.	DATE
CLASSIFIER			10/8/93
EXAMINER			10-22
TYPIST			10-23
VERIFIER			10-26
CORPS CORR.			
SPEC. HAND			
FILE MAINT.			

INDEX OF CLAIMS

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SYMBOLS

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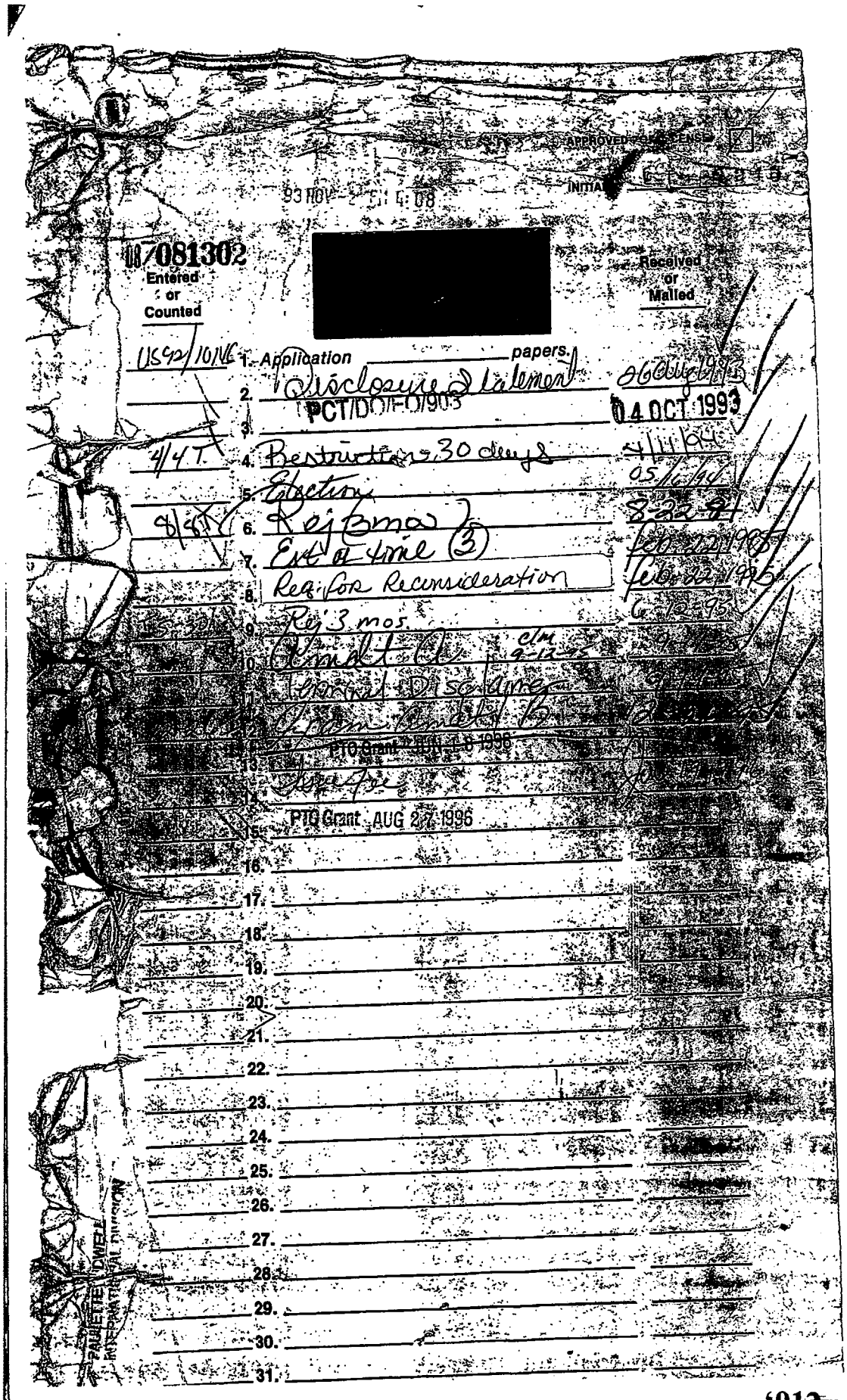
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2. Disclosure & Element
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4. Restriction 30 days
5. Election
6. Reject mo 2
7. Ext of time (3)
8. Req for Reconsideration
9. Rej 3 mos.
10. Amdt + Cl
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